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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20857

Re: Critical Path Initiative [Docket No. 2004-N-0181, 69 Federal Register (April 22, 2004)]

Dear Sir or Madam:

Amgen Inc., the world's largest biotechnology company, is focused on helping patients live longer and lead better lives through innovative research and development of treatments for grievous illness. Therefore, Amgen submits the following comments in response to the Food and Drug Administration's (FDA) request for input identifying and prioritizing the most pressing medical product development problems, and the areas that provide the greatest opportunities for rapid improvement and public health benefit.

In general, Amgen shares FDA's concern about the pace and efficiency of drug development and is hopeful that the Critical Path Initiative will achieve its intended goal of modernizing the drug development process. Before providing our feedback on the drug development hurdles that are ripe for inclusion on the Critical Path Opportunities list, there are some general points worth noting. The Critical Path will require new funding to ensure that this effort does not slow the laudable regulatory reform efforts in which FDA is currently engaged and to ensure adequate staffing. Additional staff, both project managers and scientific experts, should be hired to support the Critical Path. As Critical Path opportunities/hurdles are identified and explored there will be a need for open public debate on specific proposals and outcomes, as well as the overall progress and value of the Critical Path Initiative. We believe the Critical Path should encompass both regulatory reform and integration of new science and technology into the drug development process.

There are six drug development hurdles that Amgen has identified as potential Critical Path Opportunities and are listed in rank order as follows:

1. Consistent process for the validation of new endpoints supporting the approval of anti-cancer drugs;
2. More effective use of pharmacokinetic/dynamic models;
3. Development of pharmacodynamic assays relevant to molecular targets and pathways of disease, with shared sponsor/FDA scientific risk;
4. Improved in silico toxicity models that correlate with clinical outcomes;
5. Shared sponsor/FDA scientific risk and burden to biologically validate new safety biomarkers; and
6. Streamlining clinical trial execution.

The following criteria should be used by FDA to prioritize: 1) the ability to have an impact on the drug development process, 2) the ability to make it more standardized, and 3) give more impact to emerging technologies while still maintaining the critical focus on net patient benefit.

Each hurdle is described in further detail below:

1. Consistent process for the validation of new endpoints supporting the approval of anti-cancer drugs.

Clarification of the process to validate new endpoints for regulatory approval for anti-cancer drugs would enhance product development in numerous ways. Traditional use of "tumor responses" based solely on anatomical change has significant limitations in interpretation and reproducibility. New technologies, including imaging and the use of protein markers, offer the possibility of more direct correlation with the physiological changes effected by the new classes of therapeutics. While activities have begun on a tumor-by-tumor basis for review of available information, no concerted evidence for prospectively developing strategies for validating new endpoints has been outlined. A demonstration project to do so would lead the way for many other such activities. This proposal relates to the study of the use of physiological imaging (FDG-glucose PET scan imaging) to study the effect of a class of new therapeutics (small molecule kinase inhibitors) on tumors, and the relationship of these physiological imaging measurements with tumor response, and more importantly with changes in tumor natural history.

Validation of the use of PET scan technology to determine response and importantly, evidence for tumor progression, would greatly contribute to the design and conduct of registration trials, and bring the conduct of these trials more in line with emerging standards of clinical care in the oncology treatment community. It therefore represents a significant opportunity. Currently, drug sponsors find themselves conflicted by the design of trials which require, for example, the use of anatomical change to determine tumor progression. At the same time, many examples exist of patients whose tumors have not changed anatomically, but in whom major physiological changes are occurring which may very well correlate with patient prognosis and improved long-term outcomes. Thus, verification of these observations, and incorporation of this understanding will directly affect the approach to registration trials. This same situation is likely to become increasingly common in the cancer field.

This hurdle applies to all cancer therapeutics; the specific example which could be used relates to kinase inhibitors and the value of physiological imaging. A number of sponsors have such agents, which are being studied in, for example, gastrointestinal stromal tumors (GIST). The activity could therefore involve a class of agents in this and probably other tumors. The general approach to validate the use of this technology in these settings could be used to produce a general outline of how new technologies can be validated for use in drug development and regulatory decision-making and approval.

As indicated above, the immediate example used could be the GIST setting, or the project could also be extended to study select other solid tumors. In any case, a generally accepted approach to endpoint validation would profoundly affect all of drug development in cancer. This particular example would involve the use of physiological PET scan imaging techniques in cancer therapy development. Much information already exists from various clinical trials already conducted by pharmaceutical sponsors and cooperative groups. New agents are being introduced and new clinical trials are being initiated which involve the use of this imaging technology.

Review of currently available information could be accomplished quite quickly. In addition, sponsors could agree to contribute information from ongoing trials to some sort of agreed-upon evaluative process, which proceed over the next 24 months. An initial conclusion from this strategy should be available within this period.

FDA could identify particular agents, sponsors, academic investigators, and perhaps clinical trials which could provide data to this activity. The FDA could play a convening role to bring the various parties together to agree on a process to validate this imaging technology. It would be hoped that FDA personnel could also participate in the process, and could agree to produce some sort of summary, guideline, or points-to-consider document at the end of the project, in order to produce some sort of roadmap to the acceptance of new technologies in pharmaceutical development.

2. More effective use of pharmacokinetic/dynamic models.

A more effective use of pharmacokinetic/dynamic (PK/PD) models will enhance product development. Greater support for the continued development of bio-mathematical methods and encouraging their use will improve the process of dose optimization and candidate selection. The use of Bayesian methods to

improve estimation, model specification selection (or model blending) is not yet part of the standard drug development process. The combination of Bayesian estimation of PK/PD relationship and decision theory (as opposed to hypothesis testing) should improve a company's ability to select candidates to advance in drug development. The ability to make good decisions is improved if the critical parameters are identified and well estimated. Too often post hoc reviews of failed development efforts show that clues to failure were present early in the program.

The issues that need to be addressed include changing the regulatory environment, participating in the development of methods, and supplying data to assist in the formation of PK/PD models.

The problems identified in this document apply to virtually all potential drugs and biologics that do not have a well-established bio-mathematical model and apply to virtually all categories of disease.

Bayesian methods for decision-making and proper uses of predictive inference that combines prior information and evolving data should be encouraged. The FDA should work with industry and academia to develop improved methods and a library of case studies.

The FDA has a wealth of data, which is not in the public domain, indicating why drugs failed. The individual drugs, their nature, their target, and other characteristics are proprietary and cannot be released. However, it may be possible to aggregate and otherwise anonymize the data to help in the formation of early prior distributions for Bayesian analyses. The early discarding of unlikely drugs will enable industry to focus on more likely candidates. The "Go/No Go" decisions would remain with industry. The FDA would be a data source without disclosing private intellectual property. The details of such disclosure are very sensitive and need to be worked out with industry.

The FDA has data and other experience that should be shared with others. The activities could include convening and participating in conferences, publications of journal articles and white papers, and release of databases. The FDA could also act as an honest broker to gather information from companies and release it in ways that would not be possible for the companies. Proper respect for intellectual property and competition will be a key element.

The FDA role should be to use internal experts in collaboration with others to advance the statistical, computational, and other areas to support these areas, and the FDA could step out of its role as regulator to partner with industry as a consultant. Much progress could be made in the first 24 months of such an effort.

In terms of prioritization, the FDA should convene an expert panel that includes NIH, academic, and industry representatives to review the FDA resources for these areas. Based on this external review the FDA can determine where it can add the greatest value.

3. Development of pharmacodynamic assays relevant to molecular targets and pathways of disease, with shared sponsor/FDA scientific risk.

For most of the history of modern human therapeutics development, industry has entered early human experimentation (Phase I-IIa) with tools primarily directed at assessment of pharmacokinetic (PK) exposure, tolerability and safety. In this model, exposure levels for subsequent studies with defined clinical endpoints were typically determined by extrapolation from exposures that resulted in efficacy in animal pharmacology studies and/or dose limiting toxicities in humans. This approach has been fraught with poor predictive value of animal models with respect to human disease. In addition, the use of dose limiting toxicities has often allowed practically defined limits of exposure in humans with small molecule xenobiotics, due to off-target toxicities; this approach is much less effective with protein therapeutics. The legacy of this approach with respect to productivity and efficiency speaks for itself.

Rarely have tools been available to assess pharmacodynamic (PD) effects in early human experiments, thereby allowing an early definition of the exposure-response (i.e. PK/PD) relationship or the definition of appropriate patient populations for study. In the cases in which PD assays of this sort have been available, they have, at least in the anecdotal experience of many experts, led to more rational "Go/No Go" decisions and accurate dose selection for subsequent clinical trials. Consequently, there is now an

almost universal effort across the industry to develop such PD assays with the goal of achieving earlier, scientifically informed, readouts of biological activity, biochemical coverage and selection of appropriate patient populations. These efforts are aimed at ultimately improving the efficiency of delivering the benefits of new therapeutics to patients. It is important to note that this approach is not designed to alter current standards of animal safety assessment.

Experts also recognize the inherent scientific risk of using PD assays that have not been rigorously assessed against defined clinical and regulatory endpoints. At the same time, such experts know that patients cannot wait for such evidence before sponsors begin to innovate and implement these assays in the current environment of poor productivity. The development and application of such PD assays in the context of *a shared acceptance of the inherent scientific risk* of utilizing such tools by both industry and regulators is a clear and present hurdle for human therapeutics development.

The current scientific challenge of developing sensitive, specific PD assays relevant to a particular molecular target and/or pathway in human disease is daunting and the regulatory environment must change to align with these efforts.

The problems identified here apply to virtually all potential drugs and biologics that do not have an already existing PD surrogate marker or accepted regulatory endpoint that is easily and rapidly assessable in initial human studies. It is likely that these issues apply to many devices as well. The problems identified also apply to virtually all categories of disease.

The current scientific challenge of developing sensitive, specific PD assays relevant to a particular molecular target and/or pathway in human disease is daunting. Large investments are being made by industry toward the development of these efforts. However, a coordinated effort amongst industry, academics and government agencies to translate the marked progress in molecular and imaging technologies gained over the last two decades is required to move the field forward as rapidly as possible. Specific programs centered around diseases and/or molecular pathways currently being targeted for therapeutic intervention could be established at academic centers via government initiative (e.g. in conjunction with the proposed NIH Roadmap Regional Translational Research Centers) with potential industry sponsorship and involvement. This effort could be viewed as an extension of the multiple government sponsored efforts to facilitate the training of physician-scientists and could stress a role for these individuals in these research centers.

The regulatory environment must change to align with these efforts. Many PD assay results from early human studies will be used for internal “Go/No Go” decisions within the industry, however, even in this context, scientific input from regulators familiar with the efforts of other such endeavors could be quite useful. Although PD assays have been used in the past, the utility of such assays has not been widely disseminated. The Agency is in a unique position to have seen the results of the application of such assays and could work with those specific industrial partners to facilitate publication of this information, as mutually agreed, to enhance the acceptance of these approaches. It is particularly the case in which a molecule moves forward into registration-enabling studies at a dose range selected on the basis of an early PD assay result that the need for *a shared acceptance of the inherent scientific risk* of utilizing such tools by regulators is needed.

In addition to the fundamental acceptance of the approach, this will require regulatory agencies to develop additional expertise in the design, conductance and interpretation of PD assays; the creation of a process for an optional opportunity for industry sponsors to prospectively review PD assay strategies in a scientific setting; and a process for resolution of differences in interpretation of PD assay results, particularly with respect to dose selection for registration-enabling trials.

The FDA could play a major convening role, working with partners in agencies such as NIH and NCI to focus the efforts required. The urgency of the societal need for this approach needs to be voiced by FDA. It is not necessary for FDA to actually coordinate the proposed external research efforts, however, as they have access to the results of application of PD assays they could play a role in review of those assays that were used to establish dose ranges. They could then engage the industrial partner to determine how they could facilitate publication of such assays, if mutually agreed. The regulatory environment must change to align with these efforts such that these assays can be used to advance molecules into registration enabling trials more rapidly and that innovative products with strong PD assay

results can be approved earlier, with formal validation of traditional regulatory endpoints in the post-marketing phase. FDA could lead the global regulatory environment by taking a progressive view on the need for *a shared acceptance of the inherent scientific risk* of utilizing PD assays by both industry and regulators. This could include the development of guidance documents to help focus and direct industry efforts.

The solutions proposed above could reach initial implementation in less than 24 months, especially in light of the already existing process for the proposed NIH Roadmap Regional Translational Research Centers. Of course, the nature of the ongoing scientific challenge requires a long-term approach as well. As above, the regulatory environment must also change to align with these efforts.

The key hurdles and solutions identified above should be prioritized as parallel processes. The changes to the internal environment and processes at FDA will be more directly addressable and more rapidly achieved than the proposed research coordinating centers, which FDA should influence as effectively as possible.

4. Improved in silico toxicity models that correlate with clinical outcomes.

In order to reduce late-stage attrition due to unpredicted toxicity and to protect the health of patients, preclinical safety assessment groups need to develop and test the effectiveness of new predictive tools with a focus on how the impact of these tools bears out in the clinic. For example, FDA has been involved in supporting the development of in silico toxicity prediction tools that try to accurately assess a relationship between the structural composition of a compound with toxicity endpoints, such as in the Multicase project. Multicase uses quantitative structure-activity relationships (SAR) and expert-system contributions to identify molecular substructures that have a probability of being carcinogenic, mutagenic, irritants, teratogens, and more recently, hepatotoxins. While this program has proved useful for these endpoints and for some compound structures, there is still a significant need for the development of an expanded data sharing model that allows the larger scientific community to benefit from the information that FDA possesses regarding class effects (both biochemical and target) and increased structural alerts that goes significantly beyond the scope of the Multicase or other currently related projects. It would be useful to know the following associations:

Structural models that correlate with multiple types of toxicity: For example, Multicase predicts for only certain types of toxicity (mostly genotoxicity/carcinogenesis, hepatotoxicity), and unfortunately, even for these models, many compounds fall out of the current space of structures where high-confidence predictions can be made. Can prediction models be developed with additional, relevant data that may allow better modeling with higher confidence? Can new models around additional endpoints, i.e. neurotox and cardiotox effects and clinical observations be addressed? Can data from *in vitro* testing models (i.e. hERG, liver slices, mitochondrial assays, etc.) be added as well?

Class (target) effects or common off-target liabilities: Can blinded/generic data around certain targets, structural features or shared off-target activity be collated to supplement structural, gene/protein based predictive models as described above?

Since in silico prediction does not require compound, useful application of such models could impact all drug and biologics development processes at all stages. If used early, these models could allow initial better ranking of compounds entering *in vitro* screening assays and, more importantly, could possibly steer sponsors away from compounds that will have developmental or carcinogenic effects; since these endpoints are only assessed after long and expensive animal tests. In addition, the use of clinical correlations may allow for the prediction/modeling of some endpoints that are difficult to assess in animal models (i.e. neurotoxicity).

It is highly desirable to reduce animal testing and to protect human subjects from adverse effects in drug trials; increased development and application of excellent in silico models could impact both of these by accurately informing compound ranking early in development.

This issue applies to small molecule drugs for both on or off target effects but also would encompass on-target effects mediated by biologics. This initiative would be independent of therapeutic class.

This problem will best be approached with an assessment of ongoing related activities (industry and other) in this area for the purpose of identifying current gaps and developing short and long-term goals for model improvement. There are currently a number of private businesses that are targeted for the development of data repositories and/or mathematical in silico predictive tools. However, these data models will be most rapidly and accurately developed if populated with solid examples of preclinical (*in vitro* and *in vivo*) and clinical outcomes and include critical endpoints, such as exposure. FDA could aid in this effort through the development of a plan that will facilitate coordination of sharing anonymous sponsor data. FDA could lead the collection of generic datasets that share common off-target activities and clinical outcomes into an FDA model repository or a publicly available database tool, i.e. DEREK, for development of new in silico tools.

FDA should play a convening role of current in silico prediction experts, members of the SAR and modeling committees, and sponsors. Since FDA may be a unique place where these types of data are compiled, it is ideal for FDA to consider and propose a model to make these data generically available and to drive a solution for the data collection. However, there may be technical hurdles or sponsor sensitivities to this; therefore FDA could possibly convene working groups, such as with the International Life Sciences Institute (ILSI) or PhRMA, to study and propose solutions for model development and data collection. There would be considerable value for industry if FDA then disclosed tested models and how the output predictions fared with respect to accuracy for prediction of clinical outcome.

The proposals above would require a long-term approach to allow constant evolution of improved predictive models. However, benchmarks to gauge value for model improvement could be set in such a way that assessments of model performance are possible after input of a certain number of cases.

5. Shared sponsor/FDA scientific risk and burden to biologically validate new safety biomarkers.

Advances in genomics technologies and the simultaneous integration of large scale assays of many transcripts, protein, or metabolite endpoints has led to the development of a new field, toxicogenomics. There are two general areas of promise of toxicogenomics: 1) the potential toxicity of new compounds will be identified much earlier in the drug development process and therefore reduce the cost associated with late-stage compound attrition due to unforeseen safety concerns, and 2) possible adverse clinical outcome will be more effectively monitored due to new, sensitive and robust toxicity biomarkers. Indeed, there have been a significant number of reports in the peer-reviewed literature, patents, and new businesses that describe the elucidation of new, putative, toxicity biomarkers. These reports indicate that the safety biomarkers community is focused on elucidating predictive markers that provide the following:

- Increased sensitivity with respect to earlier detection of adverse events leading to lesions;
- Markers that better predict when an event is likely to lead to irreversible damage versus an adaptive change;
- Markers that bridge species, including across preclinical models to humans; and
- Sentinel organ toxicities (e.g. white blood cells serving as a sentinel for organ-based toxicities) for clinical monitoring.

Biological validation (determination of specificity, robustness, etc.) of these safety markers is an effort that will not be easily achieved by individual sponsor organizations. While there may be great incentive for sponsors to drive toward scenarios that allow better correlation of *in vitro* endpoints to preclinical *in vivo* models (shift toxicity-related attrition to early in the drug development pipeline), the incentive to test new toxicity markers in the clinic may not be as high, or even practical, if toxicities are somewhat rare occurrences or new markers are difficult to assay.

It is projected that there are still a significant number of compounds (at least 50%) that fall out of development due to toxicity-related issues. Therefore, methods that will allow more effective ranking for safe compounds and for bridging between non-clinical (multiple species and short-term to long-term testing) and clinical studies would be relevant to most drugs and biologics and should be ranked very high in terms of priority.

The solution for reducing this hurdle would be multi-faceted. First, it would be useful for FDA to post a public list of candidate toxicity biomarkers based on its experience from internal research, public domain, or sponsor-derived information. As certain biomarkers measurements begin to show predictive, clinical promise, new clinical assay kits would come through FDA for approval. FDA could then serve as a stakeholder to ask sponsors and physician-researchers to consider provision of monitoring on these FDA approved assays in order to address the broad questions of biological validation (i.e. reversibility, specificity, etc.). This activity may result in new industry standards and/or FDA guidance regarding the use of these assays in both preclinical safety assessment and/or clinical monitoring.

FDA should continue active collaboration in appropriate scientific and collaborative activities, including the ILSI Genomics and Biomarker Working Groups, focused on elucidating new toxicity biomarkers and assays (currently these are mostly focused in preclinical models). FDA should convene a group that assembles listings of new biomarkers from submissions or the public and then solicit/add preclinical (*in vitro* and *in vivo*) and clinical correlates to these data as they become available. Two example markers are cardiac troponin and KIM-1, proposed as early and sensitive indicators of cardiac and kidney toxicity, respectively. Both of these markers are undergoing further scrutiny and biological validation as a result of collaborative working groups with FDA and industry members. FDA should consider convening regular focused workshops on valuation of new biomarkers similar to peer working groups that are convened for pathology, alternative testing methods, etc., in order to bring appropriate attention to emerging new safety biomarkers for both the preclinical and clinical communities. The solutions above would be long term in nature, however, FDA could begin to assemble a reference list of public domain, putative biomarkers within the next six months.

6. Streamlining clinical trial execution.

We suggest that clinical trial execution be streamlined in the following four areas, listed by priority: 1) Serious Adverse Event (SAE) reporting, 2) Clinical Trial Investigators and Patient Availability, 3) Updating Regulations, and 4) E-Medical Records. Each area is outlined below in detail:

SAE Reporting:

Streamlining SAE reporting would increase the efficiency of information dissemination from sponsor to investigators and Institutional Review Boards (IRBs) and increase the usefulness of the information. The current process of disseminating safety information to investigators and IRBs is inefficient and the information content is not as useful as it could be.

Current FDA regulations, as defined in 21 CFR Part 312.32, mandate that sponsors for clinical trials of investigational products must notify the FDA and all investigators within 15 calendar days when the sponsor receives notification of significant new safety information. Investigational sites are then directly responsible for forwarding this information to their IRBs. The current regulation does allow a sponsor to propose and adopt a different reporting format of frequency, but only if the change is agreed to by the FDA in advance for each individual IND.

To increase the usefulness of this safety information, and to increase the efficiency of its distribution, the following is proposed:

- Update the current regulation such that investigators could be notified of these events in a periodic report that summarizes this safety information without requiring *advance* approval from FDA for each individual IND; and
- Update current regulations to require sponsors to notify IRBs at the same time as investigators of new safety information, rather than relying upon investigators to notify IRBs.

Streamlining SAE reporting would be relevant to all drugs, biologics and devices and could be accomplished in less than 24 months.

Clinical Trial Investigators and Patient Availability:

Clinical trial investigators and subject availability cause drug development programs to be impeded by the lack of participants. Timely, high quality execution of clinical trials is hindered by the lack of experienced investigators, poor patient awareness and access to clinical trials, which ultimately delays the availability of important new therapeutics.

Requiring certification of clinical investigators would encourage the development of an infrastructure to offer training and certification, increasing the likelihood of high quality and continuing participation of experienced clinical investigators.

Information for patients aimed at improving their awareness and understanding of clinical trials, including protection of their safety, would increase the number of study participants, speeding the development of new medicines. There have been attempts to improve patient education and awareness about clinical trials, most of limited effectiveness.

It is estimated that <5% of doctors and <10% of patients have participated in US clinical trials, yet 82% are interested if asked.

To revise requirements regarding the clinical trial investigator and subject availability, FDA should:

- Set guidance for qualification of principal investigators, sub-investigators and study coordinators and should require certification for clinical investigators and study coordinators. FDA might recognize (approve) certifying bodies, e.g. ACRP and others.
- Convene the medical community and the research community to agree on standards for patient/doctor education/awareness.
- Create or endorse programs providing a balanced view on the oversight and benefits of clinical research. Campaigns that have been done for AIDS awareness or cancer screening are very effective.

Clinical trial investigator and subject availability would be relevant to most drugs, biologics and devices and would require a long-term approach.

Outdated Regulations:

Outdated regulations create an administrative burden that is associated with the collection and reporting of some information for no apparent benefit. FDA's burden in receiving and reviewing these documents would also be reduced. Outdated regulations and guidance also prevent sponsors from applying new paradigms in clinical trial executions because it is unclear if these will be acceptable to FDA at the time of planned submission.

Another opportunity is the expansion of the end of phase 2 meeting with FDA to include discussions of how the sponsor intends to conduct the study, including quality control and quality assurance oversight (e.g. proposals for limited site monitoring, limited source document verification, limited data collection, use of electronic medical records, working with site management organizations, etc.). Commitment to report on this in the submission would enable sponsors to apply streamlined practices with prior knowledge of their acceptability. This would enable redirection of a potentially large amount of effort to additional development programs. FDA's Division of Scientific Investigations (DSI) could more effectively target their limited resources to the investigation of complaints and periodic sponsor, CRO and clinical investigator inspections rather than routine pre-approval site inspections.

The regulations governing the drug development process were written and last updated in the 1980s, while technology and organizational changes have progressed, e.g. electronic medical records and site management organizations. An update to the IND regulations would be required to add the increased scope of the end of phase 2 meeting. For sponsors no significant additional work would be needed as the quality plans are already prepared for internal purposes.

The PhRMA BioResearch Monitoring Committee and DSI are already working on a recommendation to include the sponsor's quality plan at the EOP2 meeting. This should be prioritized for broad FDA

participation and implementation. New players would need to attend the end of phase 2 meeting – representatives of DSI and the sponsor's representatives from the areas responsible for the quality plans.

The above-proposed changes would be relevant to most drugs, biologics and devices. The withdrawal of outdated requirements could be done rapidly. Updating the IND regulations (if required to enable the proposed change of scope to the end of phase 2 meeting) would require more time, but could possibly be done in less than 24 months.

E-Medical Records:

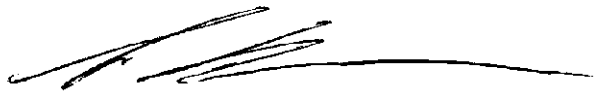
Creating e-medical records (direct to clinical database transmission of patient data) would eliminate data entry and transcription (and associated errors), and minimize source document verification. Inefficient e-medical records systems and processes used in the collection and processing of clinical trial data increases sponsor and site resource requirements to collect and clean clinical data. It also has negative impacts on study cycle time and cost, creates a duplication of effort at clinical trial sites and a large reconciliation effort.

To revise current e-medical records systems and processes, the FDA should play a convening role, first with other government agencies to determine the appropriate body to issue standards. FDA should then participate by articulating requirements for the use of such e-medical records in clinical trials. Setting standards for the collection and distribution of e-medical records would result in the adoption of those standards by sites, industry and regulatory bodies.

Revising the e-medical records systems processes would be relevant to all drugs, biologics and devices and is a long-term effort.

Amgen appreciates the opportunity to provide comments on the Critical Path Initiative and we look forward to engaging with other stakeholders in a meaningful partnership to translate today's emerging technologies into practical solutions for enhancing the drug development process.

Sincerely,



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